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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/526,430	02/13/2006	Markus Hecker	DEBE:052US/10501403	9671

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EXAMINER	
MONTANARI, DAVID A	

ART UNIT	PAPER NUMBER
1632	

MAIL DATE	DELIVERY MODE
11/28/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/526,430	HECKER ET AL.	
	Examiner	Art Unit	
	David Montanari	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *11-19* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11-19* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/16/2008 has been entered.

1. Claims 1-10 are cancelled.
2. Claim is amended.
3. The 35 USC 103(a) rejection has been withdrawn in view of the new 35 USC 103(a) rejection with additional references described below. In this regard Applicants arguments are moot.
4. The declaration by Dr. Gerhard Burckhardt has been considered but is not found persuasive.
5. Claims 11-19 are examined in the instant application.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 11-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chouini-Lalanne et al. (1998, Biochemical Pharmacology, Vol. 55, pgs. 441-446), Ajmone-Cat et al. (2001, J. of Neuroscience Res., Vol. 66, pgs. 715-722) and Gennaro A (1995, Remington: The Science and Practice of Pharmacy, 19th Ed., Mack Publishing Comp., pgs. 221-230).

For the purposes of this rejection, the term "pharmaceutical" is given no patentable weight. While the claimed formulation may be used in the manufacture of a pharmaceutical, the claimed components that comprise the formulation would be indistinguishable from the prior art below. It is noted that the instant claims contain no functional language nor indicate an intended use. The claims are drawn to a product which is a formulation comprising a nucleic acid and a nonsteroidal anti-inflammatory drug, wherein the formulation exists in a specific pH range and said drug is present in a specific concentration range.

Further "The term "formulation" or "pharmaceutical formulation" as used in the present document means the pharmaceutical form of preparation, for example, for a drug or an inoculation medium, which is administered in vivo to a human or an animal, or in vitro or ex vivo to organs, tissues or cells, consisting of one or more active ingredients and auxilliary formulation agents. Active ingredients according to the present invention are nucleic acids". (pg. 7 lines 16-24)

Given this definition provided by the specification concerning how pharmaceutical formulation should be interpreted, it appears that Chouini-Lalanne (below) would still teach the claimed invention. Claim 11 requires 1) a nucleic acid and 2) an NSAID at a pH range, if the active ingredient is nucleic acids, then it is entirely within reason that the NSAID is the auxillary

agent, and thus the teachings of Chouini-Lalanne would also encompass a pharmaceutical composition.

Chouini-Lalanne et al. teach a formulation comprising supercoiled $\phi\chi$-174 DNA in 5 mM phosphate buffer at pH 7.4 and containing 10 mM NaCl and further comprising one of four different nonsteroidal anti-inflammatory drugs (NSAID) (pg. 442, col. 1 parag. 2 bridge col. 2 parag. 1 lines 1-4 and Fig. 1). Chouini-Lalanne et al. continue to teach that the $\phi\chi$-174 DNA was complexed with either Naproxen, Ketoprofen, Tiaprofenic acid or Indomethacin (pg. 442, Fig. 1). Chouini-Lalanne et al. do not teach a formulation comprising a nucleic acid and NSAID wherein said NSAID is flurbiprofen.

However at the time of filing it was well known that NSAIDs are among the most widely used therapeutic agents. Regarding NSAIDs, Ajmone-Cat teaches that they are a well known therapeutic for the treatment of pain, fever, and inflammation. (pg. 715, col. 2 parag. 1 lines 1-3). Ajmone-Cat teaches that flurbiprofen belongs to the class of drugs known as NSAIDs and that flurbiprofen inhibits PGE_2 production (pg. 716, col.1 parag. 2) which is a prime mediator of inflammation. Ajmone-Cat et al. do not teach a formulation comprising a nucleic acid and NSAID that exhibits a pH value form pH 6.2 to pH 7.0.

Furthermore it was routine and obvious to optimize pH levels to achieve maximum drug activity. Gennaro teaches that the optimization of pH for drugs is important in four areas: drug solubility, drug stability, drug activity and drug absorption (pgs. 229 and 230). Gennaro continues that "In the broad realm of knowledge concerning the preparation and action of drugs, few, if any, variables are so important as pH" (pg. 229 col. 2 parag. 5 lines 1-3). Gennaro

continues to teach that regarding drug absorption, pH levels are important since this determines the extent to which the drug will be converted to a ionic or nonionic form. Gennaro continues that drugs that are weak acids (i.e. NSAIDs) may exist in ionized or nonionized form and may be active in one form but not the other, and thus have an optimum pH range for maximum activity.

Thus it would have been *prima facie* obvious to one of ordinary skill in the art at the time of filing to combine the teachings of Chouini-Lalanne teaching nucleic acid complexed with four different NSAID's with Ajomone-Cat teaching that NSAID's such as flurbiprofen are useful for managing inflammation to develop a formulation comprising a nucleic acid and an NSAID. Additional teaching and motivation is provided by Gennaro teaching that optimizing pH levels for drugs is of significant importance to achieve maximum activity. Further it would have been obvious at the time of filing to the ordinary artisan to perform routine experiments to determine the concentration of chloride ions and the choice of and concentration of the non-steroidal anti-inflammatory drug. In the instant claims the concentrations claimed are from 5-100 mmol/l for chloride ions and 50-250 μmol/l for the non-inflammatory drug. The concentration ranges for the chloride ions would exist in any buffer used in the manufacture in the pharmaceutical and would be of normal physiological levels as described in dependent claims 13, 14 and 19. With regard to the selection and range of the anti-inflammatory drug used in the claimed formulation the ordinary artisan, based upon the teachings of Chouini-Lalanne and Ajmone-Cat, would find it obvious to try different nonsteroidal anti-inflammatory drugs, such as indoprofen or flurbiprofen, at levels that would necessitate an anti-inflammatory action. See *In re Aller*, 105 USPQ 233 at 235 (CCPA 1955), which states "where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine

experimentation." Also see MPEP § 2144.05. In this case, the general conditions are disclosed in the prior art.

Furthermore it is well settled that routine optimization is not patentable, even if it results in improvements over the prior art. In support of this position, attention is directed to the decision in *In re Aller, Lacey, and Hall*, 105 USPQ 233 (CCPA 1955): Normally, it is to be expected that a change in temperature, or in concentration, or in both, would be an unpatentable modification. In the instant case even though the invention is drawn to using different concentrations ranges, it is not deemed patentable and an improvement over the teachings discussed above by Gennaro. Under some circumstances, however, changes such as these may impart patentability to a process if the particular ranges claimed produce a new and unexpected result which is different in kind and not merely in degree from the results of the prior art. In re Dreyfus, 22 C.C.P.A. (Patents) 830, 73 F.2d 931, 24 USPQ 52; In re Waite et al., 35 C.C.P.A. (Patents) 1117, 168 F.2d 104, 77 USPQ 586. Such ranges are termed "critical" ranges, and the applicant has the burden of proving such criticality. In re Swenson et al., 30 C.C.P.A. (Patents) 809, 132 F.2d 1020, 56 USPQ 372; In re Scherl, 33 C.C.P.A. (Patents) 1193, 156 F.2d 72, 70 USPQ 204. However, even though applicant's modification results in great improvement and utility over the prior art, it may still not be patentable if the modification was within the capabilities of one having ordinary skill in the art. Modifying the pH of the claimed pharmaceutical composition would have been within the capabilities of an ordinary artisan. In re Sola, 22 C.C.P.A. (Patents) 1313, 77 F.2d 627, 25 USPQ 433; In re Normann et al., 32 C.C.P.A. (Patents) 1248, 150 F.2d 708, 66 USPQ 308; In re Irmscher, 32 C.C.P.A. (Patents) 1259, 150 F.2d 705, 66 USPQ 314. More particularly, where the general conditions of a claim are

disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation. In re Swain et al., 33 C.C.P.A. (Patents) 1250, 156 F.2d 239, 70 USPQ 412; Minnesota Mining and Mfg. Co. v. Coe, 69 App. D.C. 217, 99 F.2d 986, 38 USPQ 213; Allen et al. v. Coe, 77 App. D. C. 324, 135 F.2d 11, 57 USPQ 136. (Emphasis added). With regards to determining experimental parameters, such as time in culture, the court has held that "[d]iscovery of optimum value of result effective variable in known process is ordinarily within skill of art (*In re Boesch and Slaney*, 205 USPQ 215 (CCPA 1980).

Response to Arguments

Applicants have filed a 37 C.F.R. 1.132 declaration by Dr. Gerhard Burckhardt on 10/16/2008. However the declaration by Dr. Burckhardt is not found persuasive in view of the new 35 USC 103(a) rejection above. As taught by Gennaro A and *In re Aller*, it would have been routine and obvious to the ordinary artisan to optimize pH levels to determine the maximum activity of a drug. Dr. Burkhardt teaches that optimization of a pH in a solution containing decoy oligonucleotides (dODNs) or DNA is critical for the delivery of these compounds to the interior of the target cell (pg. 2 parag. 2 lines 1-2). Dr. Burkhardt continues that the results of the present inventors suggest that, at a pH of 6.4, dODNs and

DNA are preferentially taken up into target cells by binding to the folate receptor (RFC1) and subsequent endocytosis and that a physiological pH of 7.4, uptake of dODNs and DNA may occur mainly through RFC1. Dr. Burkhardt continues that besides pH, structural differences of dODNs and DNA will influence the affinity for binding and translocation by both mechanisms and impact on the relative contribution of RFCI and FR to overall uptake (pg. 4 parag. 7). Dr.

Burkhardt concludes that the adjustment of pH therefore involves elaborate studies on the uptake of each individual dODN or DNA into model cells as a function of extracellular pH.

While Dr. Burkhardt has taught that optimization of pH is critical for the delivery of DNA or dODN's and that particular receptors are preferential for DNA or dODNs at certain pH levels, the claims simply require the combination of DNA with an NSAID at a pH range of 6.2 to 7.0. The art above has set forth that the optimization of pH levels is within the reach of the ordinary artisan and further that optimizing pH levels is encouraged to determine optimum solubility.

Conclusion

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to David Montanari whose telephone number is (571)272-3108. The examiner can normally be reached on M-Tr 8-6.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 1-571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

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